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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/577,489	WOOD ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36,39,40,42,43,51-60 and 64-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-36, 39-40, 42-43, 51-60, and 64-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/10; 3/31/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-36, 39-40, 42-43, 51-60, and 64-74 are pending. Applicants previously cancelled claims 1-27, 37-38, 41, 44-50, and 61-63. Claims 73-74 are new. Receipt and consideration of Applicants' remarks/arguments, amended claim set, new IDS's (submitted on December 22, 2010 and March 31, 2011) and Dr. Bosch's second 1.132 declaration submitted on March 31, 2011 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments. Applicants' new claims have necessitated new rejections and/or incorporation of these new claims into previous maintained rejections of record.

Priority

The effective filing date of the instant application is February 24, 1995.

Election/Restrictions

The species elections for asthma as the respiratory disease in a mammal and corticosteroids as the elected therapeutic agent are maintained and remain in effect.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: METHODS OF TREATING A RESPIRATORY ILLNESS BY DELIVERING LIQUID DROPLET AEROSOLS OF CRYSTALLINE NANOPARTICULATE BECLOMETHASONE HAVING SURFACE MODIFIERS ADSORBED TO THE SURFACE OF THE NANOPARTICULATE BECLOMETHASONE.

Consideration of Dr. Bosch's Second 1.132 Declaration

Dr. Bosch's declaration presents data in Table 1 concerning the composition of four different beclomethasone dipropionate (BDP) formulations comprising polyvinyl alcohol (PVAL as a surface stabilizer and labeled as: (a) Micro I (a suspension comprising micronized BDP and 2.5% PVAL which has a test volume of 1.85 ml and a mean particle size of about 10.5 microns), (b) Nano II (a dispersion comprising nanoparticulate BDP and 2.5% PVAL, which has a test volume of 1.85 ml and a mean particle size between 230-280 nm ± between 40-110 nm), (c) Nano III (a dispersion comprising nanoparticulate BDP and 0.1 % PVAL which has a test volume of 1.85 ml and a mean particle size between 230-280 nm ± between 40-110 nm. Table 2 contains data concerning the amount of BDP fraction remaining in the nebulizer and the BDP fraction reaching the impactor. The data in Table 2 indicates that the amount of BDP fraction remaining in the nebulizer was greatest for Micro I and least for Nano III, whereas the Nano II formulation had the greatest fraction of BDP reaching the impactor (i.e. ~17%) and the Micro I formulation had the lowest fraction of BPD reaching the impactor (i.e. ~8%).

Dr. Bosch's declaration at section III, Table 3, compares the particle size distribution of Applicants' nanoparticulate BDP composition to the particle size distribution of a commercially available propellant composition marketed under the VANCERIL® trademark. It is understood that Applicants' composition is a propellant-free aqueous composition, wherein the surface stabilizer is tyloxapol. Applicants' formulation was delivered from an ultrasonic nebulizer whereas the commercial application was delivered from a metered dose inhaler, a different kind of inhalation device. The comparison of Applicants' aqueous propellant-free composition delivered from an ultrasonic nebulizer to the commercially available propellant-based BDP composition marketed under the VANCERIL® trademark, delivered from a different kind of inhalation device, is considered an apples and oranges comparison regarding the deposition of the compositions contained in the two different devices (see the data in Table 4 of the second Bosch declaration).

Dr. Bosch's data is noted, but is not found persuasive or particularly relevant, because the closest prior art reference is Liversidge, which discloses nanoparticulate crystalline formulations having a surface stabilizer adsorbed to the surface of crystalline active agent. Thus, a comparison with Liversidge would be needed. Furthermore, it is noted that Applicants' claims are not limited to formulations wherein the surface stabilizer is polyvinyl alcohol or wherein the surface stabilizer is present in amounts of 2.5% w/w or 0.1 % w/w.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-36, 39-40, 51-60, and 64-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Pavord, I. et al. ("Pharmacokinetic optimisation of inhaled steroid therapy in asthma," Clin. Pharmacokinet., 1993 Aug., 25(2), abstract only), "Glaxo History" (accessed on October 24, 2008 at www/gsk/com/about/history-noflash.htm) ("Glaxo History") (of record), and the Merck Index, 10th Edition (Merck & Co., Inc.: Rahway, NJ, 1983, entry 1018 on page 144)

("MERCK"), as evidenced by Radhakrishnan (U.S. Patent No. 5,049,389) (of record) and Palmer (U.S. Patent No. 5,208,226).[1]

Applicant Claims

Applicants claim a method treating a respiratory illness in a mammal comprising the steps of (a) providing an aerosol composition comprising aqueous droplets having a particle size of less than 10 microns in diameter, wherein the droplets comprise (i) water, (ii) crystalline particles of beclomethasone having an effective average particle size of less than 1,000 nm (i.e. at least 90% of the particles have a weight average particle size of less than about 1,000 nm, as defined on pg. 16, lines 24-27 of Applicants' specification), (iii) at least one surface modifier adsorbed on the surface of the crystalline beclomethasone particles, and (b) administering the aerosol composition to the lungs of a mammal, wherein the respiratory disease is selected from the group consisting of **asthma**, emphysema, respiratory distress syndrome, chronic bronchitis, and cystic fibrosis.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Liversidge teaches that dispersible particles consisting essentially **of crystalline poorly soluble drug substance having a surface modifier adsorbed on the surface thereof exhibit** unexpectedly higher bioavailability (title; abstract; col. 1, lines 5-10; col. 2, lines 34-37; and col. 3, lines 3-9). The **effective average particle size of the invented particles is less than about 400 nm** (abstract; col. 2, lines 38-43; col. 5, lines 25-40; claims 1-5). The phrase "**effective**

[1] A copy of the complete Pavord reference is provided with this office action and is cited on the attached PTO-892.

average particle size of less than about 400 nm" is defined to mean that at least 90% of the particles have a weight average particle size of less than about 400 nm (col. 5, lines 25-28). **Preferably, at least 95% and more preferably, at least 99% of the particles have a particles size less than the effective average, such as 400 nm** (col. 5, lines 33-37). In some embodiments, the effective average particle size is less than about 100 nm (col. 5, lines 30-34). Suitable crystalline poorly soluble drugs include **anti-inflammatory agents and corticosteroids, and in preferred embodiments the drug substance is a steroid** (col. 3, lines 53-64; col. 4, lines 25-27; and claims 4-5). The drug substances are commercially available or can be prepared by techniques known in the art (col. 4, lines 13-14). Suitable surface modifiers are disclosed from column 4, line 34 through col. 5, line 12 (e.g. sodium lauryl sulfate, lecithin, Pluronic F-68 [i.e. a polymer], etc.). The surface modifiers taught by Liversidge as being suitable are essentially ones recited in Applicants' laundry list in claim 32. For example, Liversidge **explicitly identifies polyvinyl alcohol as being a suitable surface modifier** (col. 4, line 55). **Suitable amounts of surface modifier are taught to be about 0.1-10 mg per square meter surface area of the drug substance (i.e. 0.1-90% w/w, preferably 20-60% w/w, based on the total weight of the dry particle)** (col. 7, lines 10-20).

Liversidge teaches **that the nanoparticles of crystalline drug substance may be obtained by conventional milling techniques, such as air jet and fragmentation milling** (col. 5, lines 50-61). Liversidge provides the necessary guidance to obtain nanocrystalline drug particles (see col. 5, line 41 through col. 7, line 29; claims 16-20). Liversidge teaches that the compositions may be delivered to mammals (e.g. claim 15).

Merck teaches that **both beclomethasone and its diester- beclomethasone dipropionate- are suitable for the treatment of asthma** (entry 1018 on page 144).

Glaxo history teaches that in 1972 a commercial product comprising the inhaled beclomethasone dipropionate steroid was launched by Glaxo as BECOTIDE® for the treatment of asthma. **BECOTIDE® is an aqueous suspension of beclomethasone dipropionate that is conventionally administered by nebulization** (i.e. it is atomized from a nebulizer) to treat bronchial asthma, which was commercially available at the time of the instant invention, as evidenced by Radhakrishnan (col. 5, lines 43-51). Radhakrishnan's teachings also evidence that beclomethasone dipropionate is **a poorly water-soluble active agent** (col. 4, lines 22-23).

Pavord teaches that that **the recognition that asthma has a large inflammatory component has led to the use of steroids in its treatment** and **the two most widely used steroidal agents to treat asthma are beclomethasone dipropionate** and budesonide (abstract).

Palmer evidences that **beclomethasone dipropionate is an anti-inflammatory corticosteroid** (col. 1, lines 32-34).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Liversidge lacks the teaching of specific corticosteroids. This deficiency is cured by the teachings of Pavord, Merck, and Glaxo History, as evidenced by Radhakrishnan and Palmer.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify the teachings of Liversidge to utilize beclomethasone as a corticosteroid (Palmer), anti-inflammatory (Palmer), or steroid (Palmer,

Pavord, and Glaxo) selected to prepare nanoparticulate dispersions, because Liversidge explicitly indicates that suitable active agents include poorly water soluble anti-inflammatory agents, corticosteroids, and steroids and Pavord establishes that at the time of Applicants' claimed invention beclomethasone was one of the two most widely used anti-inflammatory steroids in the treatment of asthma. Furthermore, beclomethasone satisfies the requirement in Liversidge that the selected active agent is poorly water-soluble (Radhakrishnan). Thus, Liversidge and Pavord provide ample motivation for the ordinary skilled artisan to select beclomethasone as an active agent used to make nanoparticulate pharmaceutical suspensions commensurate in scope with Liversidge's teachings. Regarding the preparation of aqueous suspensions of beclomethasone an ordinary skilled artisan would have been motivated to obtain aqueous suspensions of nanoparticulate crystalline beclomethasone per Liversidge's teachings, because at the time of the instant invention beclomethasone was commercially available as an aqueous suspension marketed under the BECOTIDE® trademark and sold by Glaxo ("Glaxo History"). The BECOTIDE® product was known to contain beclomethasone dipropionate at a concentration of 50 micrograms/ml, as evidenced by Radhakrishnan. An ordinary skilled artisan would have been further motivated to use Liversidge's technology to obtain crystalline nanoparticulate beclomethasone aqueous suspensions, because said suspensions would be reasonably expected to exhibit greater local bio-availability of the beclomethasone (Liversidge) and would reasonably be expected to reach a patient's alveoli upon inhalation of an aqueous suspension of nanoparticulate crystalline beclomethasone, due to the small size of the suspended crystalline beclomethasone.

Regarding particle size of the crystalline beclomethasone and the amount of surfactant, the combined prior art teaches overlapping ranges. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Regarding the amount of beclomethasone suspended in the formulation, the commercially available BECOTIDE® product contained a concentration of beclomethasone dipropionate of 0.05% w/w, which reads on an amount of beclomethasone of about 0.1% w/w as recited in dependent claim 39. Concerning the amount of beclomethasone recited in Applicants' dependent claim 40, it is the Examiner's position that the ordinary skilled artisan would have been motivated to modify (i.e. increase or decrease) the concentration of beclomethasone based upon a patient's response to a particular dosage of beclomethasone therapy. Thus, it would have been prima facie obvious to utilize different dosages, and the ordinary skilled artisan would have arrived at dosage of from about 5% to about 30% w/w as is recited in Applicants' claim 40. Absent some demonstration of unexpected results from the claimed dosage range, the optimization of the amount of beclomethasone would have been obvious at the time of applicant's invention.

Regarding the recitation of beclomethasone and not beclomethasone dipropionate, the ordinary skilled artisan would consider the beclomethasone to be interchangeable with beclomethasone dipropionate, because both compounds are known to be suitable for the treatment of asthma, are poorly water-soluble, and are anti-inflammatory corticosteroids. Applicants' tabulated specification data is noted, and is does not demonstrate any unexpected or surprising results. Dr. Bosch's declaration data is noted, but is found unpersuasive for the reasons set forth above.

Regarding new claim 73, Liversidge explicitly identifies polyvinyl alcohol as being a suitable surface modifier. Consequently, it would have been prima facie obvious to select polyvinyl alcohol as the surface modifier. Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed March 31, 2011 have been fully considered but they are not persuasive. Applicants traverse the rejection by attacking the references individually and arguing that (i) the Examiner allegedly fails to establish a prima facie case of obviousness, because Liversidge fails to teach beclomethasone or an aerosol formulation per se and allegedly BECOTIDE® was not commercially available in the U.S. at the time of Applicants' claimed invention; (ii) the claimed invention is allegedly unobvious in view of the allegedly unexpected results in Dr. Bosch's second 1.132 declaration, (iii) Liversidge is not the closest prior art in Applicants' opinion, (iv) Applicants' alleged evidence of unexpected results for nanoparticulate crystalline beclomethasone having adsorbed upon its surface either tyloxapol or polyvinyl alcohol, allegedly provides the ordinary skilled artisan with the reasonable expectation that any other surface modifier adsorbed to the surface of said beclomethasone nanoparticles would yield the same results.

The Examiner respectfully disagrees with Applicants' traversal arguments. In response to applicant's arguments against the references individually, one cannot show nonobviousness by

attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding (i), Applicants' Exhibit A is undated and does not establish that BECOTIDE® was not commercially available at the time of Applicants' claimed invention. Furthermore, Liversidge's teachings do not require that the criterion for a drug to be suitable requires that the drug is commercially available in the U.S. Liversidge only indicates that one of his criteria is that the poorly-soluble drug needs to be commercially available. Thus, if the poorly-soluble drug is commercially available anywhere it meets this Liversidge criterion for a candidate drug to be used to make nanoparticulates within the scope of Liversidge's invention. Concerning Applicants' argument about the teaching of an aerosol formulation, this is a piecemeal argument not directed at the teachings of the combined prior art. The combined prior art establishes that beclomethasone was well-known, commercially available in the form of nebulizable formulations, and the second most widely used inhaled corticosteroid in the treatment of asthma. Therefore, the combined prior art is suggestive of the preparation of beclomethasone into nanoparticles having a surface modifier adsorbed to the surface of beclomethasone nanoparticles and its subsequent formulation into an aqueous suspension formulation for use in a nebulizer to treat asthma.

Regarding (ii)-(iv), Dr. Bosch's declaration data was not found to be persuasive, for the reasons stated above, which are herein incorporated by reference. The Examiner respectfully disagrees with Applicants' assertion that Liversidge is not the closest prior art. Finally, assuming arguendo that Applicants have demonstrated unexpected results, the great variation in the

structure, HLB values, and other chemical properties of the possible surface modifiers would not permit the ordinary skilled artisan to reasonably extrapolate Applicants' results for beclomethasone nanoparticles, wherein the surface modifier is polyvinyl alcohol or tyloxapol, to encompass or be predictive of what one would observe for all other possible surface modifiers. Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (U.S. Patent No. 5,145,684) in view of Pavord, I. et al. ("Pharmacokinetic optimisation of inhaled steroid therapy in asthma," Clin. Pharmacokinet., 1993 Aug., 25(2), abstract only), "Glaxo History" (accessed on October 24, 2008 at www/gsk/com/about/history-noflash.htm) ("Glaxo History") (of record), and the Merck Index, 10th Edition (Merck & Co., Inc.: Rahway, NJ, 1983, entry 1018 on page 144) ("MERCK"), as evidenced by Radhakrishnan (U.S. Patent No. 5,049,389) (of record) and Palmer (U.S. Patent No. 5,208,226) as applied to claims 28-36, 39-40, 51-60, and 64-73 above, and further in view of Spear et al. (U.S. Patent No. 5,525,623).

Applicant Claims

Applicants claim a method treating a respiratory illness in a mammal as described above, wherein the nebulizing step is done using a jet nebulizer (claim 42) or an ultrasonic nebulizer (claim 43).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Liversidge, Pavord, Glaxo History, Merck, Radhakrishnan, and Palmer are set forth above.

Spear teaches that **jet nebulizers and ultrasonic nebulizers are conventional means of creating aerosols for use as asthma medication** (col. 13, lines 34-40).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Liversidge lacks the teaching of a jet nebulizer or an ultrasonic nebulizer. These deficiencies are cured by the teachings of Spear.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of the instant invention to nebulize an aqueous solution comprising beclomethasone dipropionate (BDP) using either an ultrasonic nebulizer or a jet nebulizer, because both nebulizers were conventionally used to administer pharmaceutical aqueous formulations. An ordinary skilled artisan would have been motivated and would have had a reasonable expectation of nebulizing an aqueous pharmaceutical formulation, such as that resulting from the teachings of Liversidge and Radhakrishnan, with a jet nebulizer or an ultrasonic nebulizer, because said nebulizers were conventionally known to be suitable for the inhalation administration of aqueous pharmaceutical formulations and were conventionally used for this purpose (Spear). The use of a device in the matter in which said

device was intended to be used is prima facie obvious. Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed March 31, 2011 have been fully considered but they are not persuasive. Applicants traverse the rejection by reiterating the arguments presented against the first rejection under §103(a) maintained above. The Office's above rebuttal of Applicants' arguments is herein incorporated by reference. The rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-33, 39-40, 51-60, 66, 69, 72, and74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 9-11, and 13-14 of copending Application No. 10/035,324 (copending '324) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389). Independent claim 28 of the instant application is described above. Independent claim 1 of copending '324 claims a sterile, stable, nanoparticulate dispersion comprising (i) a liquid dispersion medium, (ii) nanoparticulate beclomethasone particles having an effective particle size of less than 150 nm, (iii) tyloxapol as a surface stabilizer adsorbed onto the surface of the beclomethasone nanoparticles, and (iv) optionally at least one secondary surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone.

The primary differences between the claim 28 of the instant application and claim 1 of copending '324 are that claim 1 of copending '324 does not (1) recite a method of treating a respiratory illness, (2) does not specify that the nanoparticulate beclomethasone is crystalline, (3) does not specify that the liquid dispersion medium is water, and (4) does not recite the delivery of the dispersion as droplets. Regarding (1) and (3)-(4), these deficiencies are cured by the teachings of Liversidge and Radhakrishnan, as set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses, such as asthma; that it is known to use water as a suspension/dispersion medium; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer. Regarding deficiency (2), dependent claim 11 of copending '324 evidences that it was contemplated for the beclomethasone nanoparticles to be crystalline. Thus, the formulation of

the claimed nanoparticulate dispersions of copending '324 is an obvious modification of this formulation. Regarding particle size, the particle size recited in the claims of copending '324 overlap with the particle size ranges recited in the instantly rejected claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. It is noted that tyloxapol is one of the specific surface stabilizers recited in dependent claim 32 of the instant application. Regarding the additional possible surface stabilizers, the laundry list recited in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 9 of copending '324. Regarding new claim 74, it is noted that tyloxapol is explicitly recites as a required surface stabilizer of adsorbed on the surface of the nanoparticulate beclomethasone in the claims of copending '324. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-33, 39-40, 51-60, 66, 69, 72, and 74 prima facie obvious over claims 1-7, 9-11, and 13-14 of copending Application No. 10/035,324 (copending '324) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed March 31, 2011 have been fully considered but they are not persuasive. Applicants traverse the rejection by arguing that it is proper to withdraw provisional obviousness-type double patenting rejections over later-filed applications when these rejections are the only issues remaining prior to issue. Applicants are correct that the aforementioned

withdrawal is the proper procedure wherein the only remaining issues are provisional obviousness-type double patenting rejections over later-filed applications; however, in the instant application there are multiple unresolved issues (i.e. rejections under §103(a)). Thus, withdrawal of the instant rejection would be improper at this time. The rejection is maintained.

Claims 28-33, 53-60, 66, 69, and 72 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 60-61, 64-65, 69-70, and 72-76 of copending Application No. 10/768,194 (copending '194) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389). Independent claim 28 of the instant application is described above. Independent claim 60 of copending '194 claims a method of treating a subject in need of either symptomatic or prophylactic treatment comprising administering to said subject an effect amount of sterile particulate fluticasone composition comprising (i) particles of fluticasone (i.e. an anti-inflammatory steroid) having an effective average particle size of less than 150 nm and (ii) at least one surface stabilizer.

The primary differences between claim 60 of copending '194 and claim 1 of the instant application are that claim 60 of copending '194 does not (1) specify that the disease being treated is a respiratory disease (e.g. asthma); (2) does not recite particles of beclomethasone; (3) does not specify that the particulate composition is an aqueous dispersion; and (4) does not specify that the particulate active agent is crystalline. Deficiencies (2)-(3) are cured in part by the teachings of Liversidge and Radhakrishnan set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses,

such as asthma; that it is known to use water as a suspension/dispersion medium; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer. Liversidge also establishes that anti-inflammatory steroids are suitable for incorporation into nanoparticulate dispersions (col. 3, lines 53-55 and 64; col. 4, lines 25-26; Example 1 through Example 14: col. 8, line 35 through col. 13, line 53). Regarding deficiencies (1) and (4), dependent claims 64-65 and 69 evidence that it is obvious to modify the claimed method of treatment of copending '194 to treat asthma and to utilize crystalline particulate fluticasone in the administered composition, respectively. Regarding particle size, the particle size recited in the claims of copending '194 overlap with the particle size ranges recited in the instantly rejected claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. It is noted that tyloxapol is one of the specific surface stabilizers recited in dependent claim 32 of the instant application. Regarding the additional possible surface stabilizers, the laundry list recited in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 76 of copending '194. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-33, 53-60, 66, 69, and 72 prima facie obvious over claims 60-61, 64-65, 69-70, and 72-76 of copending Application No. 10/768,194 (copending '194) in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed March 31, 2011 have been fully considered but they are not persuasive. Applicants traverse the rejection by arguing that it is proper to withdraw provisional obviousness-type double patenting rejections over later-filed applications when these rejections are the only issues remaining prior to issue. Applicants are correct that the aforementioned withdrawal is the proper procedure wherein the only remaining issues are provisional obviousness-type double patenting rejections over later-filed applications; however, in the instant application there are multiple unresolved issues (i.e. rejections under §103(a)). Thus, withdrawal of the instant rejection would be improper at this time. The rejection is maintained.

Claims 28-36 and 51-60 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 17-18 of copending Application No. 12/292,092 in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389). Independent claim 28 of the instant application is described above. Independent claims a nanoparticulate composition comprising (i) beclomethasone dipropionate particles having an average particle size of less than about 1,000 nm and (ii) at least one surface modifier.

The primary differences between the claim 28 of the instant application and claim 1 of copending '092 are that claim 1 of copending '092 does not (1) recite a method of treating a respiratory illness, (2) does not specify that the nanoparticulate beclomethasone is crystalline, (3) does not recite an aqueous dispersion medium, and (4) does not recite the delivery of the dispersion as droplets. Regarding (1)-(2) and (4), these deficiencies are cured by the teachings of

Liversidge and Radhakrishnan, as set forth above. Specifically, Radhakrishnan and Liversidge establish that beclomethasone is suitable for the treatment of respiratory illnesses, such as asthma; that it is desirable to use nanoparticulate crystalline solids in a liquid dispersion medium to obtain formulations exhibiting unexpectedly improved bio-availability; and that it is conventional to administer aqueous suspensions/dispersions as droplets via a nebulizer. Regarding deficiency (2), dependent claim 11 of copending '092 evidences that it was contemplated for the beclomethasone nanoparticles to be formulated as an aqueous dispersion. Thus, the formulation of the claimed nanoparticulate beclomethasone dipropionate of copending '092 is an obvious modification of this formulation. Regarding particle size, the particle size range recited in the claims of copending '092 overlaps with the particle size ranges recited in the instantly rejected claims of the instant application. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Regarding the possible surface stabilizers, the laundry list recited in dependent claim 32 of the instant application is substantially overlapping with the laundry list of additional surface stabilizers recited in dependent claim 17 of copending '092. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 28-36 and 51-60 prima facie obvious over claims 1-11 and 17-18 of copending Application No. 12/292,092 in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Radhakrishnan (U.S. Patent No. 5,049,389).

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed March 31, 2011 have been fully considered but they are not persuasive. Applicants traverse the rejection by arguing that it is proper to withdraw provisional obviousness-type double patenting rejections over later-filed applications when these rejections are the only issues remaining prior to issue. Applicants are correct that the aforementioned withdrawal is the proper procedure wherein the only remaining issues are provisional obviousness-type double patenting rejections over later-filed applications; however, in the instant application there are multiple unresolved issues (i.e. rejections under §103(a)). Thus, withdrawal of the instant rejection would be improper at this time. The rejection is maintained.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Davis et al. (U.S. Patent No. 5,299,566) is relevant prior art because it establishes that tyloxapol was a known surfactant (i.e. surface modifier) at the time of Applicants' claimed invention; however, Davis does not provide any rationale for picking tyloxapol as a surface modifier to be used in Liversidge's formulations other than the fact that it was known at the time of the claimed invention.

Claims 28-36, 39-40, 42-43, 51-60, and 64-74 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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